is a salt with an organic or inorganic acid.

39. The complex as claimed in claim 38, wherein said organic or inorganic acid is selected from the group consisting of acetic acid, maleic acid, hydrochloric acid and methanesulfonic acid.

40. The complex as claimed in claim 39, wherein said acid is hydrochloric acid.

41. The complex as claimed in claim 29, wherein the molar ratio between paroxetine and said cyclodextrin or cyclodextrin derivative ranges from 1:0.25 to 1:20.

42. The complex as claimed in claim 41, wherein the molar ratio between paroxetine and said cyclodextrin or cyclodextrin derivative ranges from 1:0.5 to 1:2.

43. A pharmaceutical composition containing as an active substance a pharmaceutically effective dose of a complex as defined in claim 29, in mixture with pharmaceutically acceptable diluents or excipients.

44. The pharmaceutical composition as claimed in claim 43 in solid or liquid form, for oral and for parenteral administration.--

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REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

It is respectfully submitted that new claims 29-44 are free from the objections raised by the Examiner with respect to claim 8 and also with respect to claims 1-14, 26 and 27. Accordingly, it is respectfully submitted that the objection has been overcome and should accordingly be withdrawn.

It is respectfully submitted that new claim 30, which is analogous to former claim 2, is now free from the relative terms "high solubility" and "chemical stability" and, accordingly, the rejection under the second paragraph of §112 has been overcome and should be withdrawn.

The Examiner has rejected claims 1-3 and 6-14 under §102(b) as being anticipated by Ronsen et al. WO 99/16440. This rejection is respectfully

traversed.

In particular, the Examiner asserts that Ronsen et al. disclose in Example 5 *"a free-flowing complex of paroxetine HCl and hydroxypropyl-β-cyclodextrin"*. Based on this observation the Examiner concludes that the claimed complexes, paroxetine/cyclodextrin and paroxetine/cyclodextrin derivatives, are not novel in view of Ronsen et al.

Applicants first wish to point out that Ronsen et al. is completely silent and fails to disclose or mention a complex between paroxetine and hydroxypropyl-β-cyclodextrin, but always refers to the Ronsen et al. product as an amorphous paroxetine composition, and, in particular, when referring to the product obtained by reaction with hydroxypropyl-β-cyclodextrin, it is referred to as an "amorphous paroxetine composition containing hydroxypropyl-β-cyclodextrin" (see Ronsen et al., title of Example 5, page 9, lines 26-29).

Nowhere in Ronsen et al.is evidence provided of the formation of a complex. On the contrary, Ronsen et al. refer always to a paroxetine composition stabilised by the addition of a hydroxyl bearing compound, preferably ethanol.

Even in Example 5 cited by the Examiner, Ronsen et al. disclose the reaction of paroxetine with ethanol, to which is then added hydroxypropyl-β-cyclodextrin, thus obtaining a paroxetine composition containing hydroxypropyl-β-cyclodextrin, but Ronsen et al. do not disclose or suggest the formation of any complex between paroxetine and cyclodextrin. As a matter of fact, the product obtained by Ronsen et al. in Example 5 is different from the claimed product for the following reasons.

Even if Ronsen et al. were silent about the presence or absence of ethanol in the final product of Example 5, the presence of ethanol in this product is confirmed by the specification. In fact, the starting paroxetine used in Example 5 is the paroxetine prepared as in Examples 1 or 2, that is a paroxetine which still contains, after having been vacuum dried, an amount of ethanol respectively of 4% or of 0.3% by weight. (See Ronsen et al., page 7, lines 8-9, and page 8, lines 15-16.)

Thus, the foregoing quantities of ethanol are, therefore, certainly still present in the final product of the reaction in Example 5, even if a vacuum drying step is carried out after the addition of hydroxypropyl-β-cyclodextrin. Given that in Example 5 further ethanol is added, aside from that already present in the starting paroxetine, one can certainly assume that the amount of ethanol in the final product, after vacuum drying, is even greater than the 4% or 0.3%, by weight, present in the starting paroxetine.

The claimed product which is the subject of the present invention is, on the contrary, a complex between paroxetine and cyclodextrin or a cyclodextrin derivative, which is free from ethanol.

Therefore, the foregoing serves to refute the Examiner's allegation that the claimed complexes of the present invention between paroxetine and cyclodextrin or cyclodextrin derivatives are anticipated by Ronsen et al.

Moreover, the foregoing observations of applicants are fully supported by the experimental data reported in the present application when compared with the data reported by Ronsen et al.

In fact, the amorphous paroxetine hydrochloride and hydroxypropyl-β-cyclodextrin composition according to Example 5 of Ronsen et al. has been subjected to Differential Scanning Calorimetry (hereinafter referred to as DSC) by Ronsen et al., and the results are reported in Figure 7. The thermogram in Figure 7 shows a well-defined peak at a temperature of approximately 175°C and a smaller peak at a temperature of approximately 145°C.

The thermogram obtained by the Applicant in a DSC test carried out on a complex between paroxetine hydrochloride and hydroxypropyl-β-cyclodextrin prepared according to the invention, is reported in Figure 6 of the present application. In this case, the absence of any peak at a temperature of approximately 175°C is immediately evident. In fact, this peak presumably corresponds to a product in crystalline form in which the paroxetine is bound to ethanol, and the absence of this peak provides graphic testimony to the absence of ethanol from the claimed complex.

In any event, apart from the meaning of the peak at 175°C, the profile of the two thermograms is completely different, thus proving that the present paroxetine complexes are different from the paroxetine compositions containing cyclodextrins disclosed by Ronsen et al.

Since the claims distinguish over Ronsen et al., the Examiner has failed to establish a *prima facie* case of anticipation. Accordingly, the rejection has been overcome and should be withdrawn.

As to the Examiner's rejection of the present claims under 35 U.S.C. §103 in view of Ronsen et al., applicants' respectfully traverse this rejection.

Ronsen et al. disclose paroxetine compositions containing a hydroxyl-bearing compound, preferably ethanol, and possibly one or more further hydroxyl-bearing compounds, such as the hydroxypropyl-β-cyclodextrin in Example 5, cited by the Examiner.

It is worth noting that all paroxetine compositions exemplified by Ronsen et al. contain ethanol as the only hydroxyl-bearing compound or in addition to another hydroxyl-bearing compound.

In fact, as Ronsen et al. clearly affirm in the specification, ethanol is the preferred hydroxyl-bearing compound. In particular, at page 3, first paragraph, Ronsen et al. affirm that the amount of ethanol present in the paroxetine compositions is not more than 10%, by weight, and preferably comprises between 1 and 4%, by weight. Under these conditions the paroxetine composition is in fact more stable and amenable to be manufactured and incorporated in pharmaceutical forms.

Therefore, Ronsen et al. teach that the presence of ethanol is a preferred condition for the paroxetine composition and, even when another hydroxyl-bearing compound is present, ethanol is also present (see Example 5). It is therefore evident that Ronsen et al. neither teach nor suggest in any way the present paroxetine complexes from which ethanol is absent.

The gist of the present invention is in fact to provide paroxetine complexes that are completely free from ethanol, while maintaining their stability, solubility and other advantageous properties. In fact, as discussed in the present

application, page 1 line 30 – page 2 line 21, the amounts of ethanol disclosed in the Ronsen et al. compositions are not acceptable and thus unsuitable for use in pharmaceutical compositions.

This technical problem was not even considered by Ronsen et al., which teaches completely to the contrary, namely, that the presence of a considerable amount of ethanol is preferred.

The Examiner also cites the prior art document US 5,874,447 hereinafter referred to as Benneker et al., which teaches paroxetine in the form of a free base, in the form of salts including those salts disclosed in the present application, and of hydrates of paroxetine derivatives.

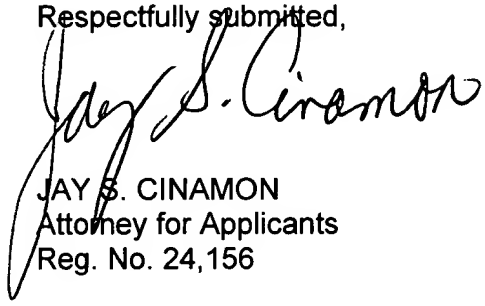
Nevertheless, Benneker et al. do not teach the complexing of paroxetine with cyclodextrins nor does it deal in any manner with the problems caused by the complexing of ethanol in paroxetine compositions. Therefore, the Benneker et al. teachings do not, by any means, nor in any manner serve to detract from the inventiveness of the present claims, when taken alone or in combination with the teachings of Ronsen et al.

It is respectfully submitted that the §103 rejection has been overcome and should be withdrawn.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,



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